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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/851,071	05/08/2001	Ann Marie Schmidt	0575/55424-Z/JPW/SHS/MVM	3248

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EXAMINER	
KAUSHAL, SUMESH	
ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 01/28/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/851,071	SCHMIDT ET AL.	
	Examiner	Art Unit	
	Sumesh Kaushal Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 November 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *17,19,20 and 35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17,19,20 and 35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *01/03/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response filed on 1/03/05 has been acknowledged.

Claims 1-6, 18, 21-24 and 36-39 are canceled.

Claims 17, 19, 35 are amended.

Claims 17, 19-20 and 35 are pending and are examined in this office action.

Applicants are required to follow Amendment Practice under revised 37 CFR §1.121. The fax phone numbers for the organization where this application or proceeding is assigned is ***571-273-8300****.*

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The references cited herein are of record in a prior Office action.

Claim Rejections - 35 USC § 103

Claims 17, 19-20 and 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gehlsen et al (JCB 106:925-930, 1988, *ref of record*) in view of Seftor et al (PNAS 89:1557-1561, 1992, *ref of record*).

The invention as claimed is drawn to a method for evaluating the ability of an agent to inhibit tumor cell spreading, wherein the agent inhibits the interaction between tumor cell and an extra cellular matrix molecule (i.e. integrin). The scope of candidate agent encompasses a molecule, which inhibits the interaction of tumor cell with an extra cellular matrix, wherein the extracellular matrix is an integrin selected from $\alpha V\beta 3$, $\alpha V\beta V$ or $\alpha I\beta II$ integrin.

Gehlsen teaches inhibition of in-vitro tumor cell invasion by Arg-Gly-Asp- (RGD) containing synthetic peptides. Regarding claim 17(a) the cited art teaches that for the invasion assays the synthetic candidate polypeptides were dissolved in DME (cell culture media) with 2% FBS, 0.1% Gentamycin and 10mM Hepes buffer. The cited art

further teaches that for cell attachment assay the peptides were dissolved in same media expect the serum was omitted (page 926, col.1 para.4). The cited art further teaches that tumor cells were cultured in DME culture media supplemented with 10%FBS and 0.1% gentamycin (page 926, col.1 para.1). The cited art further teaches the attachment of purified extracellular matrixes (i.e. Fibronectin and Vitronectin) to the polystyrene culture dishes (page 926, col.1 para. 2). Regarding claim 17(b) and (c) the cited art teaches evaluation of invasiveness of tumor cells using a membrane invasion culture system (MICS). The tumor cells (A375 melanoma, RuGli glioblastoma) were preincubated and cultured into upper compartment of the MICS chamber followed by addition of peptide-containing medium (page 926, col.2 para.1, fig-1). Regarding claim 17(d) the cited art teaches that at specific time intervals after the addition of the candidate peptide the medium from upper and lower compartments of the chamber was removed and total number of cells that passed though the membrane was evaluated (page 926, col.2 para.1, fig-1). The cited art further teaches microscopic evaluation of spreading of tumor cells in the presence of absence of candidate agents (page 926, col.2 para.2). Regarding claims 19-20 the cited art teaches metastatic melanoma cells (A375m, A375P) and RuGli glioblastoma cells (page 926, clo.2 para.3). Regarding claim 34 the cited art teaches that the MICS membrane invasion culture system used herein comprises a human amniotic basement membrane (denuded of cells), which express extracellular matrix proteins laminin, type IV collagen, fibronectin and vitronectin (page 929, col.1 para.1-3, col.2 para. 4, page 925, col.1-2). In addition the cited art further teaches the attachment of purified extracellular matrixes (i.e. Fibronectin and Vitronectin) to the polystyrene culture dishes (page 926, col.1 para. 2)

However, Gehlsen does not specifically teach the interaction of an agent that inhibit tumor cell spreading by inhibiting interaction between tumor cells and integrins $\alpha V\beta 3$, $\alpha V\beta V$ or $\alpha I\beta II$ integrin.

Seftor teaches a method for evaluating the ability of an agent to inhibit tumor invasion using an in-vitro invasion assay in context with $\underline{\alpha V\beta 3 \text{ integrin}}$ (page 1557 abstract). Regarding claim 35 the cited art explored the relationship between the

function and expression of αVβ3 integrin in A375M human melanoma cells and ability of these cells to invade in-vitro by modulating αVβ3 integrin with either antibodies or its ligand vitronectin (page 1557 col.2 para.1). The cited art teaches membrane invasion culture system (MICS), wherein in the assay was performed on the polycarbonate filter containing 10μm pores coated with Metrigel (extracellular matrix component complex). The cited art further teaches that adhesion of human melanoma cells to vitronectin, fibronectin and laminin in the presence of antibodies to various anti-integrin subunits was done according to *Gehlsen et al* specifically (page 1558, col.1 para.3). The cited art further teaches the determination of invasive potential of the treated and untreated tumor cells (page 1558, col.1 para.2, page 1559, fig-3). The cited art teaches that pretreatment of tumor cells with soluble vitronectin prior to assay resulted in increase in tumor cell invasion (page 1559, col.2 para.2). The cited art further teaches the A375M human melanoma cells express the αVβ3 integrin, wherein the αVβ3 integrin play an active role in mediating the attachment of these cells to their substratum. The cited art further teaches that αVβ3 integrin is known to bind to number of Arg-Gly-Asp (RGD) containing proteins such as vitronectin, laminin and entacti/nidogen (page 1559, col.2 para.5).

Thus it would have been obvious to one ordinary skill in the art at the time the instant invention was made to modify the invention of Gehlsen by specifically evaluating the ability of an agent that inhibits the interaction between a tumor cells and an intergrin in view of Seftor. One would have been motivated to do so identify candidate agents to inhibit tumor metastasis. One would have a reasonable expectation of success, since evaluation of a candidate compound that inhibit extracellular-matrix/tumor-cell interaction using a tumor attachment assay or a tumor invasion assays had been routine in the art the time the instant invention was made. Thus the invention as claimed is *prima facie* obvious in view of cited prior art of record.

Response to arguments

Applicant's arguments filed 11/01/04 have been fully considered but they are not persuasive. The applicant argues that Gehlsen fails to teach the step of admixing with

cell culture media an effective amount of an agent known to inhibit the interaction between a tumor cell and an extracellular matrix molecule selected from the group consisting of an amphoterin, a cadherin, an integrin or a hyaluronic acid. Gehlsen fails to teach any agent known to inhibit the interaction between a tumor cell and an amphoterin, cadherin, and integrin or hyaluronic acid. The applicant argues that combined teaching of Gehlsen and Seftor does not teach or suggest applicants invention as claimed. The applicant argues that cited art individually teach (a) identification of agents that inhibit tumor cell spreading by inhibiting the interaction between tumor cells and certain extracellular matrix molecules, none of which is recited in the claims, and (b) identification of agents that inhibit tumor invasion by modulating the $\alpha V\beta 3$ integrin. The concluded that in no way does the sum of these independent teachings demonstrate that an agent will inhibit tumor cell spreading if it inhibits the interaction between tumor cells and an integrin, an amphoterin, a cadherin or a hyaluronic acid.

However, applicant's arguments are found NOT persuasive. The arguments taken as a whole rely heavily on the deficiencies of each reference taken alone. One cannot show non-obviousness by attacking references individually where the rejections are based on combinations of references. *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co., Inc.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In instant case Gehlsen clearly teaches the method of evaluating the ability of an agent to inhibit tumor cell spreading using membrane invasion culture system (MICS) which renders the instant inventionas claimed *prima facie* obvious in view of Seftor who teaches the use of MICS for the identification of agents that binds integrin. Since Gehlsen and Seftor both teaches the use of MICS for the evaluation of agent that inhibits tumor cell invasion, there exist a clear motivation to combine the teaching of these references to identify agents that inhibits tumor invasion.

Furthermore in response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the

knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). The rationale to modify or combine the prior art does not have to be expressly stated in the prior art; the rationale may be expressly or impliedly contained in the prior art or it may be reasoned from knowledge generally available to one of ordinary skill in the art, established scientific principles, or legal precedent established by prior case law (See MPEP 2144). In this case, regarding claim 17(a) Gehlsen specifically the cited art teaches mixing of the candidate agent with cell culture media. Regarding claim 17(b) and (c) Gehlsen teaches evaluation of invasiveness of tumor cells using a membrane invasion culture system (MICS). Regarding claim 17(d) Gehlsen teaches enumeration of cell with or without the treatment of cells with candidate compounds using membrane invasion culture system. Similarly Seftor teaches a method for evaluating the ability of an agent to inhibit tumor invasion using membrane invasion culture system especially in context with $\alpha V\beta 3$ integrin. Seftor teaches the relationship between the function and expression of $\alpha V\beta 3$ integrin in A375M human melanoma cells and ability of these cells to invade in-vitro by modulating $\alpha V\beta 3$ integrin with either antibodies or its ligand. Seftor further teaches that the A375M human melanoma cells express the $\alpha V\beta 3$ integrin, wherein the $\alpha V\beta 3$ integrin play an active role in mediating the attachment of these cells to their substratum. In addition Seftor teaches that $\alpha V\beta 3$ integrin is known to bind to Arg-Gly-Asp (RGD). Therefore Gehlsen clearly teaches the method of evaluating the ability of an agent to inhibit tumor cell spreading which renders the instant invention *prima facie* obvious in view of Seftor who teaches the use of membrane invasion culture system for the identification of agents that binds integrin(s).

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sumesh Kaushal Ph.D. whose telephone number is 571-272-0769. The examiner can normally be reached on Mon-Fri. from 9AM-5PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yucel Irem Ph.D. can be reached on 571-272-0781.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to **571-272-0547.** For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199. The fax phone number for the organization where this application or proceeding is assigned is **571-273-8300.**

Sumesh Kaushal
Examiner GAU 1636

JEFFREY FREDMAN
PRIMARY EXAMINER